10 November 2016
EMA/PRAC/700146/2016 Corr[1]
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the PRAC meeting of 24-27 October 2016

This document provides an overview of the recommendations adopted by the Pharmacovigilance Risk Assessment Committee (PRAC) on the signals discussed during the meeting of 24-27 October 2016 (including the signal European Pharmacovigilance Issues Tracking Tool [EPITT][2] reference numbers).

PRAC recommendations to provide supplementary information are directly actionable by the concerned marketing authorisation holders (MAHs). PRAC recommendations for regulatory action (e.g. amendment of the product information) are submitted to the Committee for Medicinal Products for Human Use (CHMP) for endorsement when the signal concerns Centrally Authorised Products (CAPs), and to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) for information in the case of Nationally Authorised Products (NAPs). Thereafter, MAHs are expected to take action according to the PRAC recommendations.

When appropriate, the PRAC may also recommend the conduct of additional analyses by the Agency or Member States.

MAHs are reminded that in line with Article 16(3) of Regulation No (EU) 726/2004 and Article 23(3) of Directive 2001/83/EC, they shall ensure that their product information is kept up to date with the current scientific knowledge including the conclusions of the assessment and recommendations published on the European Medicines Agency (EMA) website (currently acting as the EU medicines webportal).

For CAPs, at the time of publication, PRAC recommendations for update of product information have been agreed by the CHMP at their plenary meeting (7-10 November 2016) and corresponding variations will be assessed by the CHMP.

For nationally authorised medicinal products, it is the responsibility of the National Competent Authorities (NCAs) of the Member States to oversee that PRAC recommendations on signals are adhered to.

Variations for CAPs are handled according to established EMA procedures. MAHs are referred to the available guidance. Variations for NAPs (including via mutual recognition and decentralised procedures) are handled at national level in accordance with the provisions of the Member States.

[1] Please see footnote on page 7.
[2] The relevant EPITT reference number should be used in any communication related to a signal.

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The timeline recommended by PRAC for submission of variations following signal assessment is applicable to both innovator and generic medicinal products, unless otherwise specified.

For procedural aspects related to the handling of PRAC recommendations on signals (e.g. submission requirements, contact points, etc.) please refer to the Questions and Answers on signal management.

1. Recommendations for update of the product information[3]

1.1. Cobicistat containing products: cobicistat; cobicistat, atazanavir sulfate; cobicistat, darunavir; cobicistat, elvitegravir, emtricitabine, tenofovir alafenamide; cobicistat, elvitegravir, emtricitabine, tenofovir disoproxil fumarate – Drug interaction with corticosteroids leading to adrenal suppression

Authorisation procedure	Centralised
EPITT No	18647
PRAC rapporteur(s)	Rafe Suvarna (UK)
Date of adoption	27 October 2016

Recommendation

The PRAC has reviewed the updated recommendation for corticosteroids product information and discussed specific wording for beclomethasone and all corticosteroids other than beclomethasone, as well as clarification on the formulations to which this recommendation applies. The proposed corticosteroid product information updates are applicable to all corticosteroid products, excluding products intended only for application on the skin. The MAHs of corticosteroid products should submit a variation within 3 months from the publication date of this updated PRAC recommendation, to amend the product information as described below, so that the summary of product characteristics (SmPC) and package leaflet (PL) wording is aligned for all corticosteroids (new wording underlined).

1. Cobicistat containing products

No changes have been made to the product information wording for cobicistat containing products as compared to the PRAC recommendation published on the 26th September 2016. The wording for these products remains as per the below.

SmPC of cobicistat containing products

N.B: For Evotaz, Section 4.4 warning should be maintained.

4.5. Interaction with other medicinal products and other forms of interaction

Corticosteroids primarily metabolised by CYP3A (including betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone).	Interaction not studied with any of the components of <product name>. Plasma concentrations of these medicinal products may be increased when co–administered with <product name>, resulting in reduced serum cortisol concentrations.	Concomitant use of <product name> and corticosteroids that are metabolised by CYP3A (e.g. fluticasone propionate or other inhaled or nasal corticosteroids) may increase the risk of development of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression

[3] Translations in all official EU languages of the new product information adopted by PRAC are also available to MAHs on the EMA website.

		Co-administration with CYP3A-metabolised corticosteroids is not recommended unless the potential benefit to the patient outweighs the risk, in which case patients should be monitored for systemic corticosteroid effects. Alternative corticosteroids which are less dependent on CYP3A metabolism e.g. beclomethasone for intranasal or inhalational use should be considered, particularly for long term use.

PL of cobicistat containing products

2 – What you need to know before you <take> {product name}

It is important to tell your doctor if you are taking: corticosteroids including betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone. These medicines are used to treat allergies, asthma, inflammatory bowel diseases, inflammatory conditions of the eyes, joints and muscles and other inflammatory conditions. If alternatives cannot be used, its use should only take place after medical evaluation and under close monitoring by your doctor for corticosteroid side effects.

2. Beclomethasone containing products (excluding cutaneous formulations)

Although it is noted that beclomethasone is less dependent upon CYP3A metabolism and the risk of interaction may be lower, this risk cannot be excluded. Specific wording has therefore been proposed below.

SmPC of beclomethasone containing products (excluding cutaneous formulations)

Section 4.4 or 4.5, as applicable:

Beclomethasone is less dependent on CYP3A metabolism than some other corticosteroids, and in general interactions are unlikely; however the possibility of systemic effects with concomitant use of strong CYP3A inhibitors (e.g. ritonavir, cobicistat) cannot be excluded, and therefore caution and appropriate monitoring is advised with the use of such agents.

PL of beclomethasone containing products (excluding cutaneous formulations)

- Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
- Some medicines may increase the effects of [product name] and your doctor may wish to monitor you carefully if you are taking these medicines (including some medicines for HIV: ritonavir, cobicistat).

3. All corticosteroids other than beclomethasone (excluding cutaneous formulations)

Modifications have been made in order to remove the statement relating to the receipt of case reports of Cushing's syndrome and adrenal suppression, which were not reported in association with all corticosteroids. The advice regarding considering alternative corticosteroids has also been removed. Although a similar statement has been recommended for the SmPCs of cobicistat containing products, it is considered that this broad advice on choice of corticosteroid may not be a suitable fit for all corticosteroid product information. In addition, advising on use of another corticosteroid within a steroid SmPC may be misinterpreted as infringing on clinical guidance on appropriate choice of steroid. Wording for corticosteroids other than beclomethasone has been proposed below.

SmPC of all corticosteroids other than beclomethasone (excluding cutaneous formulations) - Double strikethrough represents deletion as compared to the PRAC recommendation published on the 26th September 2016.

Section 4.4 or 4.5, as applicable:

Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. ~~Cases of Cushing's syndrome and adrenal suppression have been reported~~. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects. ~~Alternative corticosteroids which are less dependent on CYP3A metabolism eg: beclomethasone for intranasal or inhalational use should be considered, particularly for long term use~~.

PL of all corticosteroids other than beclomethasone (excluding cutaneous formulations)

- Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
- Some medicines may increase the effects of [product name] and your doctor may wish to monitor you carefully if you are taking these medicines (including some medicines for HIV: ritonavir, cobicistat).

1.2. Flucloxacillin – Acute generalized exanthematous pustulosis (AGEP)

Authorisation procedure	Non centralised
EPITT No	18773
PRAC rapporteur(s)	Margarida Guimarães (PT)
Date of adoption	27 October 2016

Recommendation

Having considered the available evidence in EudraVigilance and in the literature, and the known association between flucloxacillin and immune skin reactions, the PRAC has agreed that the MAH(s) of flucloxacillin-containing products should submit a variation within 3 months to amend the product information as described below (new text underlined).

Summary of product characteristics

4.4. Special warnings and precautions for use

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthematous pustulosis (AGEP) (see section 4.8). In case of AGEP diagnosis, flucloxacillin should be discontinued and any subsequent administration of flucloxacillin contra-indicated.

4.8. Undesirable effects

Skin and subcutaneous tissue disorders

Frequency not known: AGEP - acute generalized exanthematous pustulosis (see section 4.4)

Package leaflet

4 - Possible side effects

Other side effects (frequency not known)

Serious skin reactions

A red, scaly rash with bumps under the skin and blisters (exanthematous pustulosis).

Contact a doctor immediately if you get any of these symptoms.

1.3. Olanzapine – Restless legs syndrome

Authorisation procedure	Centralised and non centralised[4]
EPITT No	18659
PRAC rapporteur(s)	Kimmo Jaakkola (FI)
Date of adoption	27 October 2016

Recommendation

Having considered the available evidence in EudraVigilance and in the literature supporting the association of olanzapine with restless legs syndrome, the PRAC has agreed that the MAH(s) of olanzapine / olanzapine pamoate containing medicinal products should submit a variation within 2 months, to amend the product information as described below (new text underlined).

Summary of product characteristics

4.8. Undesirable effects (Table)

Nervous system disorders

Restless legs syndrome (frequency uncommon (≥ 1/1,000 to < 1/100))

Package leaflet

4 - Possible side effects

[...]

Uncommon side effects (may affect up to 1 in 100 people) include hypersensitivity (e.g. swelling in the mouth and throat, itching, rash); diabetes or the worsening of diabetes, occasionally associated with ketoacidosis (ketones in the blood and urine) or coma; seizures, usually associated with a history of seizures (epilepsy); muscle stiffness or spasms (including eye movements); restless legs syndrome; problems with speech; slow heart rate; sensitivity to sunlight; bleeding from nose; abdominal distension; memory loss or forgetfulness; urinary incontinence; lack of ability to urinate; hair loss; absence or decrease in menstrual periods; and changes in breasts in males and females such as an abnormal production of breast milk or abnormal growth.

[4] 'and non centralised' added on 8 December 2016.

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Enzalutamide	Hepatotoxicity (18754)	Eva Segovia (ES)	Supplementary information requested (submission by 4 January 2017)	Astellas Pharma Europe B.V.
Nivolumab; pembrolizumab	Transplant rejection (18781)	Brigitte Keller-Stanislawski (DE)	Supplementary information requested (submission by 4 January 2017)	Bristol-Myers Squibb Pharma EEIG; Merck Sharp & Dohme Limited

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Fluoroquinolones (for systemic use): ciprofloxacin; enoxacin; flumequine; levofloxacin; lomefloxacin; moxifloxacin; norfloxacin; ofloxacin; pefloxacin; prulifloxacin; rufloxacin	Uveitis (18686)	Martin Huber (DE)	Moxifloxacin: discussion in PSUSA; Other fluoroquinolones: routine pharmacovigilance	MAHs of fluoroquinolones for systemic use
Riociguat	Increased mortality and serious adverse events (SAEs) in patients with pulmonary hypertension (PH) associated with idiopathic interstitial pneumonias (IIP) in a single clinical trial (18681)	Julie Williams (UK)	Routine pharmacovigilance	Bayer Pharma AG